ATTACHMENT E

REMARKS

By this amendment, Applicants have amended the claims and specification in a manner which now places this application in condition for allowance. In particular, Claims 1, 3-4, 9, 11, 14 and 23 have been amended, and Claims 2, 10, 12, 15 and 17 have been canceled without prejudice. The changes to the claims are minor in nature and no new matter has been added. In addition, the specification has been amended as per the Examiner's suggestions, and an amended Abstract is provided. Applicants submit that the claims as amended are patentable for at least the reasons as set forth below.

In the Official Action, the Examiner required Correction of the Abstract, and an amended Abstract in proper form is attached hereto on a separate sheet. In addition, the Examiner objected to the specification with regard to the sequences and the drawing figures, and Applicants have overcome these objections through the present amendments to the specification, a new sequence listing, and replacement drawing sheets which make the suggested changes. Applicants have also amended the specification to refer to the priority document and government interest as set forth in 37 C.F.R. § 1.77.

In the Official Action, the Examiner made a rejection under the judicially-created grounds of obviousness-type double patenting. This rejection, insofar as applied to the claims as amended is respectfully traversed for the following reasons.

The application referred to by the Examiner, namely US Ser. No. 09/978,343, is in fact based on divisional application which was a divisional of the application which

became US Pat. No. 5,886,151, described and distinguished below. Accordingly, the arguments below with regard to the Hostetter '151 patent apply as well to the co-pending application Ser. No. 09/978,343. In both of these cases, the references relate to the whole Int1p protein, or peptide regions having no relevance to the present invention, and do not disclose or suggest the propeptide region of claim 1, much less any antibodies that can bind thereto. In short, as explained further below, the presently claimed application relates specifically to the propeptide region of the *Candida albicans* Int1p protein, and more specifically to antibodies which can bind to this region. These novel and unobvious antibodies have been shown to prevent cleavage of the propeptide which would otherwise lead to a cascade of events resulting in the activation and virulent state of a *Candida albicans* infection. In the prior works of the present first-named inventor which formed the basis of two of the references cited by the Examiner, it was not recognized that there was such a propeptide region at the specific location of amino acids 1-263 of the Int1p protein, much less that the cleavage of this region was an important factor in *Candida* virulence. These references thus do not even appreciate the problem of this virulence activation and thus cannot relate at all to the creation of antibodies that recognize this specific region and act to prevent such cleavage. Accordingly, the cited references, including US Ser. No. 09/978,343, clearly do not disclose or suggest the present claims wherein an antibody can bind specifically to the propeptide region so as to prevent the activation and virulence of *Candida* yeast.

Moreover, to the extent these references have been cited on the basis that they disclose antibodies to the whole Int1p protein, this is still irrelevant to the specific claimed invention which relates to antibodies which can bind to the specific propeptide

region, since antibodies to a whole protein will not have the same properties as antibodies which can target and bind to a specific region. Accordingly, the fact that prior or co-pending references disclose antibodies generated to the whole Int1p protein is irrelevant to the presently claimed subject matter since they will not have the properties of the present antibodies, namely the prevention of propeptide cleavage and the prevention of this mode of activation. The prior applications and patents cited by the Examiner thus do not disclose or suggest the specific claimed subject matter of an antibody which can bind specifically to the Int1p region.

Accordingly, the present claims are not disclosed or suggested in the co-pending application 09/978,343, and the Examiner's provisional double patenting rejection, insofar as applied to the claims as amended, is respectfully traversed and should be withdrawn.

In the Official Action, the Examiner rejected Claims 9 and 10 under 35 U.S.C. § 112 on the grounds of enablement, but conceded that the specification was enabling for a pharmaceutical composition comprising an isolated antibody that binds specifically to the propeptide having the amino acids 1-263 of the Int1p protein as set forth in SEQ ID NO:1. Without addressing the comments of the Examiner, Applicants have overcome this objection in that amended Claim 9 now is directed to the subject matter acknowledged as enabled by the Examiner and Claim 10 has been canceled without prejudice. The additional rejections under 35 U.S.C. § 112, second paragraph, have all been overcome in light of the amended claims.

In the Official Action, the Examiner rejected Claims 1-4 and 12-15 under 35 U.S.C. § 102(b) as being anticipated by Hostetter et al., U.S. Pat. No. 5,886,151, even

though the Examiner acknowledged that the Hostetter patent did not disclose an antibody to the specific propeptide region identified as amino acids 1-263 of the Int1p protein of SEQ ID NO:1, and that the antibody was considered to be the same since the claim was "undefined . . .by a SEQ ID number." The Examiner also stated that one would reasonably have expected the antibody of the Hostetter patent "to bind to the instantly recited propeptide" even though there is no disclosure or suggestion of such an antibody in the Hostetter patent, and indeed, no prior antibody was known or suggested which has the properties of the present claimed antibody, namely the ability to prevent the cleaving of the propeptide so as to control the activation and virulence of *Candida* infections. As indicated above, the mere fact that antibodies to the whole Int1p protein were previously known is entirely irrelevant to the present invention since indeed the antibodies raised to the whole protein will not have the same properties of antibodies raised to specifically recognize the propeptide, and indeed the ability of the antibodies of the present invention to prevent cleaving of the propeptide and control activation and virulence of *Candida* outbreaks was not known or suggested in the prior art.

In the Official Action, the Examiner also rejected Claims 1, 9 and 10, 11, 12 and 17 under 35 U.S.C. § 103(a) as being unpatentable over Hostetter et al., U.S. Pat. No. 5,886,151. However, these rejections related not to Claim 1, but to the subject matter in the dependent claims. As indicated above, the Hostetter patent does not disclose or suggest the specific antibody of the present claims, namely an antibody to the propeptide region of the Int1p protein, amino acids 1-263 of SEQ ID NO:1, and indeed at the time of the earlier Hostetter patent, the present inventors, including the first-named inventor in the Hostetter patent, were not aware of the specific propeptide region

nor its function in being cleaved so as to activate the infection process, much less antibodies to the propeptide region which could be used to prevent such cleaving. Accordingly, the prior Hostetter patent does not disclose or suggest the presently claimed invention, and the rejections on the basis of this reference, insofar as applied to the claims as amended, in particular amended Claim 1 and its dependent claims, are respectfully traversed and should be withdrawn.

Finally, the Examiner rejected Claim 1 under 35 U.S.C. § 102(b) by either the White et al. 1990 article or the Hostetter et al. 1991 article. However, once again, neither of these articles disclose or suggest the specific antibody of the present claims, namely an antibody which binds to the propeptide region of the Int1p protein which can prevent the cleaving of the propeptide. Moreover, the Examiner acknowledged that this rejection was only asserted since the prior claims were not identified by SEQ ID number. The present claims now include a reference to the specific amino acids which constitute the propeptide region of the Int1p protein, and it is clear that none of the cited references make any disclosure or suggestion of this specific propeptide region, much less its role in activation and virulence of *Candida albicans* or the creation and use of isolated antibodies raised thereto in preventing cleavage and activation.

In short, none of the cited references disclose or suggest the specific antibodies of the presently claimed application, namely an antibody which can bind to the propeptide of the Int1p protein. Accordingly, the outstanding rejections, insofar as applied to the claims as amended, are respectfully traversed and should be withdrawn.

In light of the amendments and arguments as set forth above, the present application has been placed in condition for allowance and such action is earnestly solicited.

END REMARKS

ATTACHMENT A

Marked-Up Replacement Paragraphs

Page 1, prior to the first section, please insert the following new sections:

C1

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims the benefit of U.S. provisional application Ser. No. 60/237,082, filed September 28, 2000.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under Contract Number AI25827 awarded by the NIH. The government has certain rights in the invention.

Please replace the following numbered paragraphs with the marked-up versions below:

C2

[0017] Fig. 3 is a schematic representation of the activation of a general proprotein convertase which shows the presence of a signal peptide, the propeptide, an inactive subtilisin and P-domain, and the manner of activation. This figure includes DHNS (SEQ ID NO:3) and DHNRGDS (SEQ ID NO:4)

[0018] Fig. 4 is a schematic representation of the int1p protein as compared to a generic proprotein convertase which illustrates the clipping of the Int1p propeptide which is cleaved to become a superantigen at the same time the subtilisin regions are activated as well. This figure includes DHNS (SEQ ID NO:3) and DHNRGDS (SEQ ID NO:4)

C3

[0026] ~~Fig. 12 illustrates~~Figures 12A and 12B illustrate the flow cytometry of surface-exposed domains of Int1p when *C. albicans* blastospores are grown to exponential phase in the absence (left panel) or presence (right panel) of 2 units of heparin. X axis represents log-scale fluorescence; Y axis represents percent yeasts fluorescing. Hatched area - fluorescence with anti-INT600. Gray area-fluorescence

with anti-CBS2. Fluorescence of *C. albicans* cells incubated with rabbit IgG serves as control - dotted line.

C3

[0027] ~~Fig. 13 is a Western blot~~ Figures 13A, 13B and 13C are Western blots of supernatants from *INT1*-expressing *S. cerevisiae* grown in the absence or presence of heparin and probed with rabbit polyclonal antibodies to the Int1p amino terminus (anti-INT600), to the second divalent cation binding site (anti-CBS2), or to the RGD domain (anti-RGD).

C4

[0031] Fig. 17 shows the MHC-II Binding Sites in the Int1p protein, and in Mycoplasma arthritidis, as disclosed in *J. Exp. Med.* 183:1105-1110 (1996), incorporated herein by reference. This figure includes FVQNL (SEQ ID NO:5), NNVVFTNKELE (SEQ ID NO:6), FAQLLNKNNEV (SEQ ID NO:7) and NSEPE (SEQ ID NO:8)

C5

[0040] As shown in the schematic drawing Figs. 3 and 4, activation of "subtilisin-like" proprotein convertases occurs in the Int1p protein which ultimately leads to the cleaving of the propeptide and the activation of the virulent form of the microorganism. In Fig. 3, the schematic analysis of the Int1p protein shows the presence of a signal peptide, the propeptide, an inactive subtilisin and the P-domain. The processing or "P-domain" is employed to clip the propeptide at the carboxy terminal side of dibasic residues, thereby releasing the propeptide. Exposed D-H-N-S (SEQ ID NO:3) active site residues assume the subtilisin serine protease conformation. This amino terminal processing is shown further in Fig. 4 wherein the original form of Int1p is transformed by the clipping of the propeptide, which includes heparin binding region 155-169, and which is cleaved to become a superantigen at the same time the subtilisin regions are activated as well. P Domain subtilisin motifs from a variety of proteins are compared as shown in Fig. 5. Fig. 6 shows a comparison of the high-affinity heparin binding site of *Mycobacterium tuberculosis* heparin-binding hemagglutin adhesin (HBHA) with the heparin-binding site of the Int1p protein of *Candida albicans*.

[0093] Most proprotein convertases exhibit several highly conserved features including a propeptide domain, distinguished by a canonical cleavage site just C-terminal to a pair of dibasic amino acids, most frequently KR or KK. A catalytic domain spans approximately 330 amino acids with an active site sequent of D-H-N-S [Asp-His-Asn-Ser] (SEQ ID NO:3), in which the initiating D is followed by a DX. This DDX motif has been shown in other systems (e.g., integrins) to be a recognition site for the binding of the RGD tripeptide; however, this interaction has never been explored with proprotein convertases. Catalytic domains may occur singly or in tandem. Lastly, a processing domain (or P-domain) also contains a D-H-N-S (SEQ ID NO:3) motif, but in six of the seven know SPC's, an RGD tripeptide is intercalated between the N and the S. The RGD motif is essential for cleavage of the propeptide; site-directed mutagenesis of the RGD tripeptide inhibits zymogen processing and mis-directs cellular trafficking of the unprocessed protein.

ATTACHMENT C

Marked-Up Replacement Abstract

ABSTRACT OF THE DISCLOSURE

[00107] Antibodies and agents which can bind to the propeptide of the Int1p protein of yeast microorganisms such as *Candida albicans* are provided which can be useful in methods for treating or preventing infections arising from such microorganisms. Microorganisms expressing the Int1p protein, such as *C. albicans* and *S. cerevisiae*, have shown an ability to immunomodulate host cells which allows infections of these microorganisms ~~enhances~~ to thrive and become virulent. ~~In accordance with the present invention,~~The peptide regions involved in the activation of the Int1p protein are isolated and targeted so as to provide a method of disrupting ~~said~~ activation and allow for treatment or prevention of infection by microorganisms expressing the int1p protein. In one preferred embodiment of the invention, an antibody or agent which can bind to the propeptide of the Int1p protein from *C. albicans* is utilized in methods to prevent or treat infections caused by *C. albicans* or other microorganisms expressing the Int1p protein.